98-390317/34 B03 FABR 97.01.15
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97.01.15 97FR-000336 *(98.07.17)* C07D 401/12, A61K 31/495 (C07D 211:64, 295:155, 401/12) (C07D 211:52, 401/12, 295:15) (C07D 211:16, 401/12, 295:15)

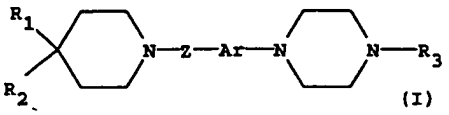
New piperidinyl-substituted N-aryl-piperazine derivatives - used as selective 5-HT-1D and 5-HT-1B receptor antagonists, e.g. for treating depression, anxiety or cancer

C98-118101

Addnl. Data: HALAZY S, LAMOTHE M, JORAND L C

B(7-D5, 7-D11, 14-H1, 14-J1) .4

Piperidinyl-substituted N-aryl-piperazine derivatives of formula (I) and their hydrates, solvates and bio-precursors, including geometric and optical isomers and their mixtures (especially racemates), are new.



(I)

R_1 = R'1, OR'1, SR'1, NHR'1, COR'1, CH(OH)R'1 or $CH_2R'_1$;

R'1 = Ar';
Ar' = phenyl, naphthyl or pyridinyl (all optionally substituted by one or more of 1-5C alkyl, halo, OH, OR_4, SR_4, CF_3, CH_2CF_3, NO_2, CN, COR_4, $COOR_4$, NHR_4, $NHCOR_4$, $NHCOOR_4$, $NHSO_2R_4$ and SO_2R_4);
R_4 = H or 1-5C alkyl;
R_2 = Cl, F, Br, OH, NH_2, CN, NO_2, R'2, OR'2, SR'2, NHR'2, COR'2, CH(OH)R'2, COOR'2, NHCOR'2, NHCOOR'2, $NHSO_2R'_2$ or OCONHR'2;
R'2 = 1-5C alkyl, Ar' or Ar'-alkyl;
provided that if R_1 = OR'1, SR'1 or NHR'1 then R_2 = R'2, COOR'2, COR'2 or CH(OH)R'2;
Z = $CO(CH_2)_nO$, $CO(CH_2)_nNH$, $(CH_2)_mO$, $(CH_2)_mNH$, $CO(CH_2)_pCONH$, $(CH_2)_pCONH$, $CO(CH_2)_pNHCONH$, $(CH_2)_mNHCONH$, $CO(CH_2)_pOCONH$, $(CH_2)_mOCONH$, $CO(CH_2)_pNHCOO$ or $(CH_2)_mNHCOO$;
n = 0-8;
m = 2-8;
p = 1-8;

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Ar = arylene such as phenylene or naphthylene, optionally substituted by one or more of 1-6C alkyl, 1-6C alkoxy and halo;
R_3 = 1-6C alkyl.

MORE SPECIFICALLY

Ar = phenylene (optionally mono-substituted by OMe, Me or Cl in the ortho-position to the piperazinyl group); or naphthylene with the piperazinyl group in the 1-position and the -Z-piperidinyl group in the 7-position;
R_3 = Me;
Z = $CO(CH_2)_nO$, $CO(CH_2)_nNH$, $(CH_2)_m$ or $(CH_2)_mNH$;
R_1 = R'1 or $CH_2R'_1$;
R_2 = CN, OH, OR'2, R'2, NH_2 or NHR'2.

USE

(I) are 5HT-1D and 5HT-1B receptor antagonists, and are useful for treating or preventing disorders associated with serotonin, e.g. CNS and cell proliferation disorders. They are especially used for treating or preventing depression, compulsive-obsessive disorders, anxiety, panic attacks, schizophrenia, aggression, bulimia, alcoholism, pain, neuro-degenerative diseases (e.g. Parkinson's and Alzheimer's disease) or cancer (all claimed).

Other disorders which may be treated include movement disorders, agoraphobia, memory disorders, dementia, amnesia, appetite disorders, sexual dysfunction, endocrine disorders (e.g. hyperprolactinaemia), vasospasm, hypertension and gastrointestinal disorders involving motility and secretion.

Daily dose for adults is 0.001-1 (preferably 0.005-0.25) g, preferably orally. Claimed compositions containing (I) optionally also contain a further antidepressant active agent, especially milnacipran and/or a 5HT-1A antagonist.

ADVANTAGE

(I) are potent and selective antagonists of human 5HT-1D and 5HT-1B receptors, having especially high selectivity for such receptors relative to 5HT-1A, 5HT-1C, 5HT-2, α_1, α_2 and D_2 receptors.

PREPARATION

The following processes are claimed.

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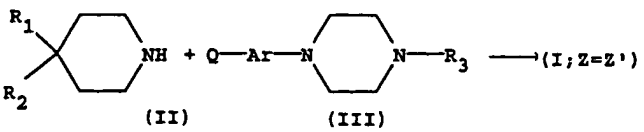
(a)

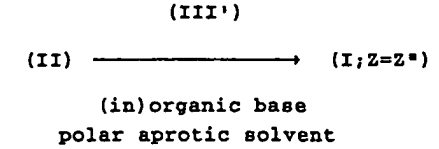


(II) (III) (I;Z=Z')

Q = L-Z'-;
Z' = $CO(CH_2)_nO$, $CO(CH_2)_nNH$, $CO(CH_2)_pCONH$, , $CO(CH_2)_pNHCONH$, $CO(CH_2)_pOCONH$ or $CO(CH_2)_pNHCOO$,

provided that n is other than 0;
L = OH, Cl or residue of an activated COOH group.

(b)



(III') = as for (III) but with Q = X-Z"-;
Z" = $(CH_2)_mO$, $(CH_2)_mNH$, $(CH_2)_pCONH$, $(CH_2)_mNHCONH$, $(CH_2)_mOCONH$ or $(CH_2)_mNHCOO$;

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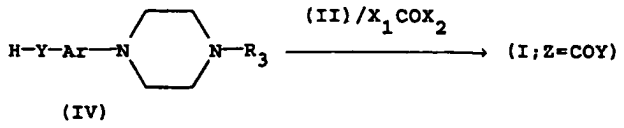
X = leaving group such as Cl, Br, I, tosyloxy, mesyloxy or OSO_2CF_3.
(c)



(IV)

Y = O or NH;
X_1, X_2 = leaving groups such as Cl or $OCCl_3$.

EXAMPLE

A solution of 491 mg 4-methoxy-3-(4-methylpiperazin-1-yl)-aniline and 200 ml pyridine in 20 ml CH_2Cl_2 was treated under N_2 at 0°C with a solution of 240 mg triphosgene in 30 ml CH_2Cl_2, stirred at room temperature for 30 minutes, treated with a solution of 413 mg 4-cyano-4-phenylpiperidine and 200 ml pyridine in 10 ml CH_2Cl_2 and stirred for 12 hours at room temperature. Work-up and chromatographic purification gave 558 mg (61%) of (4-cyano-4-phenyl-piperidin-1-yl)-N-(4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl)-amide, which was converted into the fumarate by reaction with fumaric acid in methanol.

BIOLOGICAL DATA

(I) had IC_{50} values of 10-1,000 nM for inhibition of the sumatriptan-stimulated incorporation of labelled thymidine into C_6 type glial cells transfected with the 5HT-1D and 5HT-1B receptor genes. No specific values for individual compounds are given. (AB)
(48pp2400DwgNo.0/0)

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